REMARKS/ARGUMENTS

1. Claims 1, 3 and 6-7 are pending. Claim 1 is currently being amended to incorporate phenotypic limitations fully supported in the specification as originally filed, for example, at page 32, lines 15-25. Claim 6 is currently being amended to recite that the claimed mouse cells are isolated from the mouse of claim 1, which, as the Examiner will appreciate, is supported by the specification, for example, as found from page 6, line 33, to page 7, line 2. Claim 7 is currently being amended to be an independent claim incorporating all the limitations of claim 1, and is fully supported by the specification as originally filed, for example, from page 22, line 17, to page 23, line 14. Accordingly, as the Examiner will appreciate, no new matter is added by the amendments.

2. Written Description – 35 U.S.C. § 112, first paragraph.

Claims 1, 3, 6, and 7 stand rejected for inadequate written description on the basis that the claims encompass genetically modified mice generated by nuclear transfer which is a "highly unpredictable" field in which the mice obtained would "likely ... exhibit phenotypes unrelated to the RAMP1 gene disruption." The Examiner further states that Applicants' previous amendment and response filed September 18, 2003, wherein the claimed mice were amended to have the phenotypic limitation of nondetectable RAMP1 activity, does not overcome the written description rejection because the specification fails to describe "the phenotype of the mouse derived by somatic cell nuclear transfer." Applicants traverse this rejection, but note that independent claims 1 and 7 are also being amended to recite the phenotypic limitation that the claimed mice, or mice generated by the claimed ES cells, which are homozygous for disruption of the RAMP1 gene, exhibit elevated aminotransferase, alanine aminotransferase, or creatine kinase activity. This phenotypic limitation is incorporated into all pending claims.

To the extent that this rejection focuses upon the method of making the claimed mice, Applicants traverse this rejection and note that the claims at issue are to compositions of matter and not methods.

> When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in a way in which the claimed composition is made that may arise after the patent application is filed. See United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, [1251; 9 USP2d 1461,1465] (Fed. Cir. 1989); In re Koller, 613 F.2d 819, 824-25 [204 USPQ 702, 707] (Fed. Cir. 1980); see also In re Hogan 559 F.2d

> 595, 606 [194 USPQ 527, 538] (C.C.P.A. 1977). Instead, section 112 only requires the Court to determine whether the specification conveys to one of ordinary skill in the art as of 1984 that Dr. Lin invented the subject matter claimed in the patents-in-suit. Reiffin, 214 F.3d 1342,1346 [Reiffin v. Microsoft Corp., 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917 (Fed. Cir. 2000)]. The written description inquiry, therefore, focuses on a comparison between the specification and the invention referenced by the terms of the claim – not a comparison between how the product was made as disclosed in the patent and future developments of this process that might alter or even improve how the product is made.

Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc., 314 F.3d 1313, 1331-32, 65 USPQ2d 1385 (Fed. Cir. 2003) (citing Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc., 126 F. Supp. 2d, 69, 150; 57 USPQ2d 1449, 1508 (D.C. Mass., 2001).

Therefore, alternative methods of making the claimed subject matter (e.g., nuclear transfer), beyond those actually disclosed to make the mice, are not relevant to the written description requirement.

As the Examiner will appreciate, the specification provides adequate written description of the claimed mice and ES cells capable of generating the mice, as being currently amended, by providing definitive structural and functional phenotypic description (see specification, for example, from page 5, line 24, to page 6, line 7, Figure 2, and from page 27, line 21, to page 33, line 2) such that one skilled in the art could readily identify a genetically-modified mouse encompassed by the claims and recognize that Applicant was in possession of the claimed genus.

For all of the above reasons, Applicants respectfully request entry of the amendment and reconsideration of the Office Action mailed December 24, 2003.

3. Enablement – 35 U.S.C. § 112, first paragraph.

A. Claims 1 and 3 remain rejected for lack of enablement on the basis that the specification only "teaches a mouse generated by targeted gene disruption of the RAMP1 gene in ES cells wherein the mouse exhibits altered aminotransferase, alanine aminotransferase, and creatine kinase activities, which are associated with muscle and/or liver cell damage (pages 32, lines 16-20)." The Examiner asserts that the previously added limitation to claim 1, wherein the claimed subject matter relates to mice and cells exhibiting non-detectable RAMP1 activity, is insufficient to overcome this rejection because "failing to exhibit RAMP1 polypeptide activity

does not require that the mouse exhibit any attributes that would enable the skilled artisan to use said mouse." Applicants disagree with this assertion, and note that the lack of detectable RAMP1 activity is precisely the phenotypic feature that one skilled in the art would exploit, for example, to use the claimed subject matter as a negative control to test whether a compound modulated RAMP1 activity (see specification, for example, at page 33, lines 5-17). However, Applicants also note that all claimed subject matter, as currently being amended, relates to mice, cells isolated from mice, and ES cells capable of generating genetically-modified mice, wherein the mice exhibit the phenotype of elevated aminotransferase, alanine aminotransferase, or creatine kinase activity. Accordingly, Applicants respectfully request entry of the amendment and reconsideration of the Office Action mailed December 24, 2003.

B. Claims 6 and 7 stand rejected for lack of enablement on the basis that the specification "fails to teach making a totipotent murine ES cell other than mouse totipotent ES cells." While Applicants respectfully disagree with this statement, claims 6 and 7 are currently being amended to limit claimed subject matter to mouse cells. Therefore, Applicants respectfully request entry of the amendment and reconsideration of the Office Action mailed December 24, 2003.

C. Applicants acknowledge the withdrawal of the rejection of claims 1, 3, 6, and 7 regarding enablement of any RAMP1 gene in view of Applicants' amendment filed September 18, 2003.

4. Indefiniteness. Applicants acknowledge the withdrawal of the rejection of claim 6 in view of Applicants' amendment filed September 18, 2003.

5. Obviousness. Claim 1 remains rejected on the basis that the general methodology teachings of homologous recombination disclosed in Capecchi, in view of the RAMP1 sequence disclosed in Hussman, render the claim obvious. With regard to Applicants' previous comments on this (as to how one skilled in the art would not be able to predict, prior to its actual generation, whether a RAMP1 knockout mouse and mouse cell would be viable and could be made, as illustrated by the number of embryonic lethal targets (7 out of 32 targets) listed in the survey of phenotypes for knockout mice targeted for disruption of druggable targets (Zambrowicz, Nature Reviews – Drug Discovery 2: 38-51, 2003, previously submitted)), the Examiner asserts that the targets "are not representative of the vast number of knockout mice that have been generated," and cites the database of 300 knockout mice, as found at www.bioscience.org, in which only 39 were reported to have prenatal mortality. While

Applicants disagree with the basis for the Examiner's rejection (noting, first, that no basis has been provided to support the contention that druggable targets are somehow different from other targets with respect to embryonic lethality following disruption, and, second, that the Examiner has failed to account for the number of embryonic lethal knockouts that fail to ever get reported because they are "failed" experiments), this basis for rejection is now moot given the claims as currently being amended.

Applicants note that all claimed subject matter, as now being amended, relates to mice, cells isolated from mice, and ES cells capable of generating mice, wherein the mice exhibit elevated aminotransferase, alanine aminotransferase, or creatine kinase activity. Thus, Applicants note that information on knockout technology and the RAMP1 gene, as arguably provided by combination in Capecchi and Hussman, in no way discloses or suggests to one skilled in the art that, should the claimed genetically-modified mice and mouse cells be successfully made, that such mice would exhibit a phenotype of elevated aminotransferase, alanine aminotransferase, or creatine kinase activity. Accordingly, Applicants respectfully request entry of the amendment and reconsideration of the Office Action mailed December 24, 2003.

6. Applicants believe that the amendments hereinabove to the claims place the Application in condition for immediate allowance. Therefore, entry of the amendments hereinabove and reconsideration of the Office Action mailed December 24, 2003 are respectfully requested. Such prompt and favorable action is earnestly solicited.

Respectfully submitted,

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